The Selegiline Transdermal System (Emsam)

A Therapeutic Option for the Treatment Of Major Depressive Disorder

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ABSTRACT

Although monoamine oxidase inhibitors (MAOIs) at one time represented the mainstay of therapy for major depressive disorder (MDD), the risk of acute hypertensive reactions following the ingestion of tyramine-rich foods and the consequent need to restrict dietary tyramine represent a barrier to their use. In this article, we present an overview of the efficacy and safety of a transdermal formulation of the MAOI selegiline for the treatment of MDD. Transdermal delivery of selegiline at the effective dose of 6 mg every 24 hours eliminates the need for a tyramine-restricted diet. Our emphasis on potential drug–drug interactions and contraindications should be useful to prescribers who counsel patients with MDD.

INTRODUCTION

Despite the wide availability of clinically efficacious therapies for depression, as many as 50% of patients who begin treatment do not respond to it, and up to 30% do not gain benefits from a range of therapy regimens.[1] Reflecting their established efficacy, safety, and widespread clinical use, oral monoamine oxidase inhibitors (MAOIs) were the mainstay of major depressive disorder (MDD) therapy during the 1950s. However, reports of serious adverse events, including acute hypertensive reactions following ingestion of tyramine-rich foods such as aged cheese,[2] and the subsequent need to restrict dietary intake of tyramine with MAOI therapy led to a decline in the use of these agents. Despite these barriers, many psychiatrists believe that MAOIs are currently underused in clinical practice,[3,4] particularly given their proven efficacy in atypical depression,[5–9] psychotic depression,[10,11] dysthymic disorder,[12] treatment-resistant depression,[13–17] and bipolar depression.[14,18,19] As a result, considerable efforts have been made to develop an MAOI antidepressant that can overcome these limitations.

Transdermal selegiline (Emsam, Somerset/Bristol-Myers Squibb) is the first therapeutic option of its kind to be approved by the Food and Drug Administration (FDA) for the treatment of MDD. Given the primary role of pharmacists and physicians in advising patients on the use of concomitant medications, we outline the efficacy, safety, potential interactions, and contraindications of the selegiline transdermal system (STS).

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A NOVEL DELIVERY SYSTEM

The STS has a unique delivery system that was designed to overcome the limitations associated with oral MAOIs, particularly those relating to dietary constraints. Monoamine oxidase (MAO) in the gastrointestinal (GI) tract (predominantly the MAO-A isoenzyme) is a key enzyme in tyramine metabolism. When MAO-A in the GI tract is sufficiently inhibited, tyramine cannot be metabolized; it enters the systemic circulation, resulting in an elevation of blood pressure and potentially leading to a hypertensive crisis.[2,20]

The pharmacokinetic and pharmacodynamic properties of the STS permit the inhibition of MAO-A and MAO-B in the central nervous system (CNS) while limiting MAO-A inhibition in the intestinal mucosa and liver. At the effective selegiline dose of 6 mg every 24 hours, the system's dermal application enables targeted inhibition of MAO enzymes in the CNS without significantly increasing sensitivity to dietary tyramine, thus eliminating the need for dietary modifications of foods containing tyramine at this dose.[21]

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EFFICACY AND SAFETY

Efficacy

The efficacy and tolerability of the STS at a dose of 6 mg every 24 hours in MDD has been demonstrated in several short-term and long-term placebo-controlled clinical trials. It was also assessed in a flexible-dose study.

Bodkin and Amsterdam[22]

In a short-term, randomized, double-blind study of six weeks' duration (n = 177), patients with moderate-to-severe depression received either the STS (6 mg/24 hours) or placebo once daily. Because this was the first large study of the STS for MDD, subjects followed a tyramine-restricted diet. At the study's endpoint, the STS showed significantly greater efficacy, compared with placebo, according to:

- the 17-item Hamilton Rating Scale for Depression (HAM-D-17) (–8.7 ± 7.5 vs. –6.1 ± 6.7; $P = 0.01$).
- the 28-item HAM-D Scale (–11.2 ± 9.8 vs. –7.6 ± 8.6; $P = 0.004$).
- the Montgomery–Åsberg Depression Rating Scale (MADRS) (–9.8 ± 11.5 vs. –5.7 ± 9.1; $P = 0.005$).

Greater reductions in mean scores occurred as early as the first week of STS treatment, compared with placebo.[22] In addition, significantly more STS patients achieved a reduction of 50% or more in both total HAM-D-17 scores (37.5% vs. 22.7%; $P = 0.04$) and HAM-D-28 scores (37.5% vs. 22.7%; $P = 0.03$) at the study's endpoint than the placebo group. Moreover, more patients scored below 8 on the HAM-D-17 with the STS, compared with placebo (22.7 vs. 11.4%; $P = 0.04$).

Efficacy was also evaluated with the Clinical Global Impression (CGI) Severity of Illness and Improvement measures. Greater global improvement was observed with the STS than with placebo (42% vs. 27%; $P = 0.03$).

Feiger et al.[23]

In a second, short-term, eight-week study (n = 265), patients with moderate-to-severe depression received a flexible STS dose of 6 to 12 mg/24 hours or placebo once daily with no dietary tyramine restrictions. Patients receiving the STS experienced greater reductions at the endpoint (eight weeks) in:

- HAM-D-28 scores (STS baseline = 28.3 ± 3.7, mean change = –11.1 ± 8.6; placebo baseline = 28.6 ± 4.0, mean change = –8.9 ± 9.1; $P = 0.03$).
- MADRS scores (STS baseline = 29.3 ± 4.2, mean change = –11.6 ± 9.8; placebo baseline = 29.3 ± 4.2, mean change = –8.6 ± 10.3; $P = 0.02$).
- Inventory for Depressive Symptomatology-Self Rated scores (STS baseline = 37.3 ± 8.8, mean change = –13.9 ± 12.1; placebo baseline = 37.6 ± 9.4, mean change = –10.6 ± 12.5; $P = 0.03$), compared with placebo.

In this study, patients receiving the STS also showed significant improvements from baseline, compared with placebo, for the secondary outcome of HAM-D Bech-6 scores (representing core depressive symptoms) (STS baseline = 12.4 ± 1.3, mean change = –5.5 ± 4.3; placebo baseline = 8.5 ± 4.3, mean change = –4.1 ± 4.2; $P = 0.01$).

Amsterdam[24]

In a further short-term study, 289 patients received either the STS 6 mg/24 hours (n = 145) or placebo (n = 144) once daily for eight weeks. Patients did not need to follow a tyramine-restricted diet.

At the study's endpoint, the STS group experienced significantly greater reductions in HAM-D-28 scores (18.6 ± 9.4 vs. 21.2 ± 9.3; $P = 0.39$) and in MADRS scores (18.0 ± 10.0 vs. 21.7 ± 9.9; $P = 0.03$). HAM-D-17 scores were also better at the endpoint but not significantly (STS = 14.7 ± 7.2 vs. placebo = 16.3 ± 7.1; $P = 0.06$).

Amsterdam and Bodkin[25]

In a long-term, double-blind, placebo-controlled relapse-prevention study, 322 patients who had responded to 10 weeks of open-label STS 6 mg/24 hours were randomly selected to receive either transdermal selegiline 6 mg/24 hours or placebo once daily for up to 52 weeks. No dietary tyramine restrictions were required.

Relapse was defined as meeting these criteria on two consecutive visits:

- a HAM-D-17 score of 14 or higher
- a CGI score of 3 or higher with a two-point increase from the baseline score
- criteria for MDD, as defined in the *Diagnostic Statistical Manual of Mental Disorders* (*DSM-IV*)

At week 26, significantly fewer STS-treated patients (16.8%) than placebo-treated patients (29.4%) experienced a relapse ($P = 0.005$). STS efficacy was maintained throughout the study, with significantly fewer STS patients experiencing relapse at week 52 (17%), compared with placebo patients (30.7%; $P = 0.003$).

Patients who completed the study also experienced a significantly longer time to relapse over 52 weeks, compared with those receiving placebo ($P = 0.005$).

Safety and Tolerability of the STS Patch

In the acute[22–24] and long-term[25] studies already outlined, transdermal selegiline was well tolerated, and there were no significant differences in treatment withdrawal rates between STS and placebo groups. The most common adverse events that occurred with the long-term STS use included application-site reactions, infection, insomnia, and headache.[25] The occurrence rate of adverse events with the STS was similar to that seen in the placebo patients except for reactions at the application site. In a 52-week study,[25] a trend toward an increased incidence of insomnia in STS-treated patients was also observed.

Application-site reactions, which generally consisted of mild-to-moderate itching, redness, and swelling, were the most problematic adverse events associated with STS patches. However, these reactions were usually transient, of short duration, and mild to moderate in intensity, and they usually resolved within several hours after patch removal.

The patch should not be applied to an area of skin that is irritated, broken, scarred, or calloused, and a new application site should be selected with each new patch to avoid a reaction at the site. Cases of persistent irritation should be referred to a physician.

No cases of hypertensive crisis were reported in any of the controlled clinical trials.

CLINICAL APPLICATIONS: ADDRESSING UNMET NEEDS

For the substantial number of patients with depression, including those who do not respond adequately to, or who are intolerant of, existing antidepressant therapy, alternative options are needed. The clinical data regarding the STS patch demonstrate both its acute and long-term safety and efficacy in patients with MDD.

In particular, as the first antidepressant available for transdermal administration, STS offers the benefits of an effective MAOI without the need for dietary modifications at the lowest effective dose (6 mg/24 hours). The STS may therefore offer a promising alternative therapeutic option for patients with only partial or no response to initial MDD therapy.

Although the STS provides several advantages over oral MAOIs (i.e., minimal interaction with dietary tyramine and possibly a more rapid onset of therapeutic action), additional studies are needed in order to further evaluate this

population and their responsiveness to the system.

PRACTICAL CONSIDERATIONS

Dosage

STS patches are available in three doses: 6, 9, and 12 mg every 24 hours. No dietary modifications are required at the recommended starting and target doses for the 6-mg/24 hour regimen.

Higher STS doses of 9 and 12 mg/24 hours are also effective, but studies were not designed to evaluate improved efficacy at higher doses. Based on the more limited data available for the doses of 9 and 12 mg/24 hours, food effects cannot be ruled out; therefore, patients receiving these doses should follow dietary modifications that include the avoidance of tyramine-rich food and beverages during treatment and for up to two weeks after therapy has been completed. Dietary modifications should also be followed for two weeks after a dose reduction to 6 mg/24 hours.[26]

No dose adjustment is necessary for patients with mild-to-moderate renal or hepatic impairment. The recommended daily dose for elderly patients (65 years of age and older) is 6 mg/24 hours; careful monitoring of these patients is necessary if the dose is increased further.[26]

Applying the Patch

The STS patch should be applied every 24 hours, and it should be changed at the same time each day. Patients should remove the old patch before applying a new one. The patch is applied to dry, smooth skin on the patient's upper chest or back (below the neck and above the waist), the upper thigh, or to the outer surface of the upper arm. A new site should be chosen each time the patch is changed.

The application site should be free of hairy, oily, irritated, or broken tissue, and the patch should not be placed where the patient's clothing is tight, because this can cause the patch to be rubbed off.

DRUG–DRUG INTERACTIONS AND CONTRAINDICATIONS

Despite the widespread use of MAOIs over the past 50 years, their pharmacokinetic interactions have yet to be fully elucidated.[27,28] The potential for interactions between the STS and alcohol, alprazolam (Xanax, Pfizer), ibuprofen, levothyroxine (Synthroid, Abbott), olanzapine (Zyprexa, Lilly), and warfarin (Coumadin, Bristol-Myers Squibb) have been the subject of several studies, none of which has confirmed an altered pharmacokinetic profile of either selegiline or the test agent. However, the potential for drug–drug interactions has been identified with carbamazepine (Tegretol, Novartis) and some sympathomimetic agents. As with other MAOIs, these agents are contraindicated in patients using the STS (Table 1).[26]

Carbamazepine can cause a decrease in drug exposure, although slightly increased levels of selegiline and its metabolites were seen following a single application of the STS at 6 mg/24 hours in subjects who had received carbamazepine 400 mg/day for 14 days.[26] The clinical relevance of these findings is unknown.

For the sympathomimetic agents, pharmacokinetic studies have shown that giving the STS at a dose of 6 mg/24 hours with phenylpropanolamine (PPA) 25 mg every four hours for 24 hours does not affect the pharmacokinetics of PPA. However, there was a higher incidence of significant blood pressure elevations with the STS plus PPA than with PPA alone, suggesting a possible pharmacodynamic interaction.[26] Giving the STS at a dose of 6 mg/24 hours for 10 days with pseudoephedrine (60 mg three times daily) did not affect the pharmacokinetic properties of pseudoephedrine.[26]

As with other MAOIs, the STS should not be administered with cold products or weight-reducing preparations that contain vasoconstrictors, including amphetamine and other sympathomimetic agents (see Table 1). Other medications are also contraindicated with the STS, such as:

- selective serotonin reuptake inhibitors (SSRIs).
- selective norepinephrine reuptake inhibitors (SNRIs).
- tricyclic antidepressants.
- St. John's wort.
- meperidine (Demerol, Sanofi-Synthelabo).
- analgesic agents: tramadol (Ultram, PriCara), methadone (Dolophine, Roxane), and propoxyphene (Darvon, aaiPharma/Xanodyne).
- cold or cough preparations containing dextromethorphan.

Oral selegiline and other MAOIs should not be used concomitantly with the STS (see Table 1).

Contraindications with other antidepressants are largely related to CNS toxicity ("serotonin syndrome"), which has been reported in case studies.[29] Serotonin toxicity is characterized by neuromuscular excitation (hyperreflexia, myoclonus, rigidity), autonomic stimulation (hyperthermia, tachycardia, tremor, flushing), and an altered mental state (anxiety, agitation, confusion).

Serotonin toxicity can be mild, with features that might not be a concern to the patient; moderate, with toxicity causing significant but not life-threatening distress; or severe, consisting of a medical emergency characterized by rapid onset of severe hyperthermia, muscle rigidity, and multiple organ failure.[29] An increase in CNS toxicity has been observed in case reports of patients who received an MAOI with or shortly after the administration of SSRIs.[30–37]

Two case reports in individual patients have described similar reactions with oral selegiline and SSRIs.[38,39] However, in patients with Parkinson's disease, oral selegiline at the approved dose of 5 mg twice daily was well tolerated when it was administered with sertraline (Zoloft, Pfizer), paroxetine (Paxil, GlaxoSmithKline), or fluoxetine (Prozac, Lilly).[40–42] In general, the quality of the evidence is poor and further studies are required to examine drug interactions with antidepressant medications.

Owing to their irreversible inhibition of MAO, the physiological effects of MAOIs may persist for up to three weeks after they are discontinued.[43] As such, a 14-day washout period is recommended before alternative antidepressant therapy is initiated in order to prevent potentially serious pharmacodynamic interactions. Similar precautions should be taken when patients are switched from one MAOI to another, although more rapid switches (from one to eight days) have been safely performed.[44,45]

The practice of avoiding the narcotic analgesic meperidine in patients receiving MAOIs is based on data from case reports with nonselective MAOIs[46–52] and from one case report with oral selegiline and meperidine (pethidine).[51] For those patients receiving MAOIs, morphine is considered the narcotic analgesic of

choice.[53–55] Notably, alternative therapeutics are available for other contraindicated medications (Table 2).[56]

For example, Tylenol Cold Daytime and Nighttime are contraindicated because of their inclusion of pseudoephedrine and dextromethorphan; however, Tylenol Cold Relief as well as the nighttime formula contains acetamino-

Table 1 Medications Contraindicated for Patients Using the Selegiline Transdermal System

Class	Example of a Contraindicated Drug*	Evidence Level for Class†
Narcotic analgesics	Meperidine (Demerol)	Probable
Analgesics	Tramadol (Ultram) Methadone (e.g., Dolophine) Propoxyphene (e.g., Darvon, Darvocet)	Not noted‡
Muscle relaxant	Cyclobenzaprine (Flexeril)	Not noted‡
Antitussive agents (found in cold and cough medications)	Dextromethorphan (active ingredient in Zicam Cold and Flu, Coricidin HBP Cough/Cold (for high blood pressure), Tylenol Cold Daytime and Night-time, Mucinex DM), Benadryl Allergy and Cold Caplets	Suspected
Vasoconstrictors (found in cold products and weight-reducing preparations)	Pseudoephedrine (active ingredient in Tylenol Cold, Sudafed Tablets) Phenylephrine (active ingredient in Zicam Cold and Flu, Benadryl allergy/sinus headache) Phenylpropanolamine Ephedrine	Established
Selective serotonin reuptake inhibitors	Fluoxetine (Prozac) Sertraline (Zoloft) Paroxetine (Paxil)	Probable
Dual serotonin and norepinephrine reuptake inhibitors	Venlafaxine (Effexor) Duloxetine (Cymbalta)	Probable
Tricyclic antidepressants	Imipramine (Tofranil) Amitriptyline (Elavil)	Suspected
Tetracyclic antidepressant	Mirtazapine (Remeron)	Not noted‡
Monoamine oxidase inhibitors	Oral selegiline (Eldepryl) Isocarboxazid (Marplan) Phenelzine (Nardil) Tranylcypromine (Parnate)	Not noted‡
Antianxiety agent	Buspirone (BuSpar)	Not noted‡
Amino ketone agent	Bupropion HCl (Wellbutrin and Zyban)	Suspected
Herbals	St. John's wort	Not noted‡
Antiepileptics	Carbamazepine (e.g., Tegretol, Biston, Calepsin, Carbatrol) Oxcarbazepine (Trileptal)	Suspected
Amphetamines	Dextroamphetamine (e.g., Dexedrine) DL-amphetamine (Benzedrine)	Suspected
Methylphenidates	Dexmethylphenidate (Focalin) Methylphenidate (e.g., Ritalin)	Suspected

*The recommended washout period for contraindicated medications is about one to two weeks (four to five half-lives) before and two weeks after STS treatment. One exception is fluoxetine, which requires a five-week washout period prior to STS therapy. Note that more rapid switches of one to eight days have also been performed safely for monoamine oxidase inhibitors.

†Level of evidence for interaction with MOAI class based on *Facts and Comparisons* 4.0, in which "established" = proven to occur in well-controlled studies; "probable" = very likely but not proven clinically; "suspected" = may occur, some good data, but needs more study; "possible" = could occur, but data are limited.

‡Evidence level not noted by *Facts and Comparisons* 4.0.

Table 2 Over-the-Counter Medications Not Contraindicated For Patients Using the Selegiline Transdermal System

Class	Example
Analgesics	Motrin IB Caplets
Antitussive agents (in cold and cough medications)	Zicam Cold Remedy, Corcidin HBP Cold and Flu, Tylenol Cold Relief, Mucinex
Antihistamines, antitussive agents (in cold and cough medications)	Benadryl Allergy Kapseals, Claritin 24 Hour Allergy Tablets, Tavist Allergy Tablets, Zicam Cold Remedy, Corcidin HBP Cold and Flu, Tylenol Cold Relief, Mucinex
Cough and cold products	Tylenol Cold Relief, Zicam Cold Remedy, Benadryl Allergy, Advil Caplets, Coricidin HBP Cold and Flu Tablets, Comtrex Maximum Strength Sore Throat Relief Liquid, Tylenol Chest Congestion Cool Burst Caplets, Vicks VapoRub, Robitussin Chest Congestion Guaifenesin Syrup USP, Mucinex Extended-Release Tablets
Antihistamines	Benadryl Allergy Kapseals, Claritin 24 Hour Allergy Tablets, Tavist Allergy Tablets

phen and diphenhydramine and represents an alternative for patients needing the STS. Because the brand names of these medications can be similar, the pharmacist or physician can advise patients to check the contents of the product as well as the brand name for contraindicated components. This is especially important, because the ingredients of over-the-counter products may change, necessitating that patients check each purchase.

The STS patch is also contraindicated for patients undergoing elective surgery involving general anesthesia; in this situation, the STS should be discontinued at least 10 days before the procedure. If surgery is required earlier, agents such as benzodiazepines, mivacurium (Mivacron, Abbott), morphine, and codeine may be used with caution. In addition, local anesthetics containing sympathomimetic vasoconstrictors should be avoided.

Although the data do not suggest the need for a modified diet at the STS 6-mg/24-hour dose, because of the limited data available, ingesting foods and beverages containing tyramine is contraindicated for patients receiving the STS at higher doses and for up to two weeks after therapy is stopped or reduced to the 6-mg/24-hour dose.[26]

Table 3 presents some tyramine-rich foods and beverages to avoid, including aged or fermented meat, poultry and fish, aged cheeses, broad bean pods, concentrated yeast extract, most soybean products, and all varieties of tap beer.[57] As with other antidepressants, the concomitant use of alcohol with the STS is not recommended.

CONCLUSION

The clinical data regarding the Emsam patch demonstrate both its short-term and long-term safety and efficacy in patients with MDD. In particular, the STS

Table 3 Dietary Modifications Needed for Patients Using the Selegiline Transdermal System 9 mg and 12 mg/24 hours

Class	Foods and Beverages to Avoid	Acceptable Foods
Meat, poultry, fish	Air-dried, aged, and fermented meats, sausages and salamis (cacciatore, hard salami, mortadella); pickled herring; and any spoiled or improperly stored meat, poultry and fish (e.g., foods that have undergone change in coloration or odor or have become moldy); spoiled or improperly stored animal livers	Fresh meat, poultry, and fish, including fresh processed meats (e.g., lunch meats, hot dogs, breakfast sausage, and cooked sliced ham)
Vegetables	Broad (fava bean) bean pods	All other vegetables
Dairy	Aged cheeses	Processed cheeses, mozzarella, ricotta cheese, cottage cheese, yogurt
Beverages	All varieties of tap beer, and beers that have not been pasteurized so as to allow for ongoing fermentation	As with other antidepressants, the concomitant use of alcohol is not recommended; bottled and canned beers and wines contain little or no tyramine
Miscellaneous	Concentrated yeast extract (e.g., Marmite), sauerkraut, most soybean products (soy sauce, tofu), over-the-counter supplements containing tyramine	Brewer's yeast, baker's yeast, soy milk, commercial chain restaurant pizzas prepared with cheeses low in tyramine

Note: No dietary restrictions are required for patients using the 6 mg/24-hour selegiline transdermal system (Emsam).
Data from Shulman KI, Walker SE. *Psychiatr Ann* 2001;31:378–384.[57]

provides several advantages to orally administered MAOIs, including freedom from dietary tyramine modifications at a dose of 6 mg/24 hours and a favorable side-effect profile.

Given their positions in the pathway of care, pharmacists and physicians play a major role in counseling patients about the potential for drug interactions and alternative treatments. Accordingly, awareness of potential interactions that may be encountered with the STS will optimize the use of this MAOI as an alternative for patients with MDD.

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REFERENCES

1. Thase ME. Therapeutic alternatives for difficult-to-treat depression: A narrative review of the state of the evidence. *CNS Spectr* 2004;9(11):808–816, 818–821.
2. Blackwell B, Marley E. Interactions of cheese and of its constituents with monoamine oxidase inhibitors. *Br J Pharmacol Chemother* 1966;26(1):120–141.
3. Nierenberg AA. Treatment choice after one antidepressant fails: A survey of northeastern psychiatrists. *J Clin Psychiatry* 1991;52(9):383–385.
4. Fiedorowicz JG, Swartz KL. The role of monoamine oxidase inhibitors in current psychiatric practice. *J Psychiatr Pract* 2004;10(4):239–248.
5. Nierenberg AA, Alpert JE, Pava J, et al. Course and treatment of atypical depression. *J Clin Psychiatry* 1998;59(Suppl 18):5–9.
6. Davidson J RD, Pelton S. An outpatient evaluation of phenelzine and imipramine. *J Clin Psychiatry* 1987;48(4):143–146.
7. Liebowitz MR, Quitkin FM, Stewart JW, et al. Phenelzine v. imipramine in atypical depression: A preliminary report. *Arch Gen Psychiatry* 1984;41(7):669–677.
8. Liebowitz MR. Depression with anxiety and atypical depression. *J Clin Psychiatry* 1993;54(Suppl):10–14; discussion, 15.
9. Quitkin FM, Rothschild R, Stewart JW, et al. Atypical depression: Unipolar depressive subtype with preferential response to MAOIs. *In:* Kennedy SH, ed. *Clinical Advances in Monoamine Oxidase Inhibitor Therapies.* Washington, DC: American Psychiatric Press; 1994.
10. Janicak PG, Pandey GN, Davis JM, et al. Response of psychotic and nonpsychotic depression to phenelzine. *Am J Psychiatry* 1988;145(1):93–95.
11. Davidson JR, McLeod MN, Kurland AA, et al. Antidepressant drug therapy in psychotic depression. *Br J Psychiatry* 1977;131:493–496.
12. Vallejo J, Gasto C, Catalan R, et al. Double-blind study of imipramine versus phenelzine in melancholias and dysthymic disorders. *Br J Psychiatry* 1987; 151:639–642.
13. McGrath PJ, Stewart JW, Nunes EV, et al. A double-blind crossover trial of imipramine and phenelzine for outpatients with treatment-refractory depression. *Am J Psychiatry* 1993;150(1):118–123.
14. Thase ME, Mallinger AG, McKnight D, et al. Treatment of imipramine-resistant recurrent depression, IV: A double-blind crossover study of tranylcypromine for anergic bipolar depression. *Am J Psychiatry* 1992;149(2):195–198.
15. Nolen WA, van de Putte JJ, Dijken WA, et al. Treatment strategy in depression, II. MAO inhibitors in depression resistant to cyclic antidepressants: Two controlled crossover studies with tranylcypromine versus L-5-hydroxytryptophan and nomifensine. *Acta Psychiatr Scand* 1988;78(6):676–683.
16. Amsterdam JD, Hornig-Rohan M. Treatment algorithms in treatment-resistant depression. *Psychiatr Clin North Am* 1996;19(2):371–386.
17. Amsterdam JD, Shults J. MAOI efficacy and safety in advanced stage treatment-resistant depression: A retrospective study. *J Affect Disord* 2005;89(1–3):183–188.
18. Himmelhoch JM, Thase ME, Mallinger AG, et al. Tranylcypromine versus imipramine in anergic bipolar depression. *Am J Psychiatry* 1991;148(7):910–916.
19. Thase ME, Trivedi MH, Rush AJ. MAOIs in the contemporary treatment of depression. *Neuropsychopharmacology* 1995;12(3):185–219.
20. Blackwell B, Marley E, Price J, et al. Hypertensive interactions between monoamine oxidase inhibitors and foodstuffs. *Br J Psychiatry* 1967;113:349–365.
21. Robinson DS. Monoamine oxidase inhibitors: A new generation. *Gen Psychopharmacol* 2002;36(3):124–138.
22. Bodkin JA, Amsterdam JD. Transdermal selegiline in major depression: A double-blind, placebo-controlled, parallel-group study in outpatients. *Am J Psychiatry* 2002;159(11):1869–1875.
23. Feiger AD, Rickels K, Zimbroff DL, et al. Selegiline transdermal system for the treatment of major depressive disorder: An eight-week, double-blind, placebo-controlled, flexible-dose titration trial. *J Clin Psychiatry* 2006;67:1354–1361.
24. Amsterdam JA. Double-blind, placebo-controlled trial of the safety and efficacy of selegiline transdermal system without dietary restrictions in patients with major depressive disorder. *J Clin Psychiatry* 2003;64(2):208–214.
25. Amsterdam JD, Bodkin JA. Selegiline Transdermal System (STS) in the prevention of relapse of major depressive disorder: A 52-week, double-blind, placebo-substitution, parallel-group clinical trial. *J Clin Psychopharmacol* 2006;26(6):579–586.
26. Emsam (Selegiline Transdermal System), prescribing information. Available at: www.bms.com. Accessed September 2006.
27. Mallinger AG, Smith E. Pharmacokinetics of monoamine oxidase inhibitors. *Psychopharmacol Bull* 1991;27(4):493–502.
28. Baker GB, Urichuk LJ, McKenna KF, et al. Metabolism of monoamine oxidase inhibitors. *Cell Mol Neurobiol* 1999;19(3):411–426.
29. Isbister GK, Buckley NA, White IM. Serotonin toxicity: A practical approach to diagnosis and treatment. *Med J Austral* 2007;187(6):361–365.
30. Sternbach H. Danger of MAOI therapy after fluoxetine withdrawal. *Lancet* 1988;2(8615):850–851.
31. Kline SS, Mauro LS, Scala-Barnett DM, et al. Serotonin syndrome versus neuroleptic malignant syndrome as a cause of death. *Clin Pharm* 1989;8(7):510–514.
32. Ooi A, Mai M, Ogino T, et al. Endocrine differentiation of gastric adenocarcinoma: The prevalence as evaluated by immunoreactive chromogranin A and its biologic significance. *Cancer* 1988;62(6):1096–1104.
33. Heisler MA, Guidry JR, Arnecke B. Serotonin syndrome induced by administration of venlafaxine and phenelzine. *Ann Pharmacother* 1996;30(1):84.
34. Klysner R, Larsen JK, Sorensen P, et al. Toxic interaction of venlafaxine and isocarboxazide. *Lancet* 1995;346(8985):1298–1299.
35. Phillips SD, Ringo P. Phenelzine and venlafaxine interaction. *Am J Psychiatry* 1995;152(9):1400–1401.
36. Weiner LA, Smythe M, Cisek J. Serotonin syndrome secondary to phenelzine–venlafaxine interaction. *Pharmacotherapy* 1998;18(2):399–403.
37. Beasley CM Jr, Masica DN, Heiligenstein JH, et al. Possible monoamine oxidase inhibitor–serotonin uptake inhibitor interaction: Fluoxetine clinical data and preclinical findings. *J Clin Psychopharmacol* 1993;13(5):312–320.
38. Shad MU, Marsh C, Preskorn SH. The economic consequences of a drug–drug interaction. *J Clin Psychopharmacol* 2001;21(1):119–120.
39. Suchowersky O, deVries JD. Interaction of fluoxetine and selegiline. *Can J Psychiatry* 1990;35(6):571–572.
40. Toyama SC, Iacono RP. Is it safe to combine a selective serotonin reuptake inhibitor with selegiline? *Ann Pharmacother* 1994;28(3):405–406.
41. Waters CH. Fluoxetine and selegiline: Lack of significant interaction. *Can J Neurol Sci* 1994;21(3):259–261.
42. Richard IH, Kurlan R, Tanner C, et al. Serotonin syndrome and the combined use of deprenyl and an antidepressant in Parkinson's disease. Parkinson Study Group. *Neurology* 1997;48(4):1070–1077.
43. Cooper AJ. Tyramine and irreversible monoamine oxidase inhibitors in clinical practice. *Br J Psychiatry Suppl* 1989(6):38–45.
44. Marangell LB. Switching antidepressants

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for treatment-resistant major depression. *J Clin Psychiatry* 2001;62(Suppl 18):12–17.
45. Szuba MP, Hornig-Rohan M, Amsterdam JD. Rapid conversion from one monoamine oxidase inhibitor to another. *J Clin Psychiatry* 1997;58(7):307–310.
46. Jounela AJ, Kivimaki T. Possible sensitivity to meperidine in phenylketonuria. *N Engl J Med* 1973;288(26):1411.
47. Mitchell RS. Fatal toxic encephalitis occurring during iproniazid therapy in pulmonary tuberculosis. *Ann Intern Med* 1955;42(2):417–424.
48. Papp C, Benaim S. Toxic effects of iproniazid in a patient with angina. *Br Med J* 1958(5103):1070–1072.
49. Shee JC. Dangerous potentiation of pethidine by iproniazid, and its treatment. *Br Med J* 1960;5197:507–509.
50. Vigran IM. Dangerous potentiation of meperidine hydrochloride by pargyline hydrochloride. *JAMA* 1964;187:953–954.
51. Zornberg GL, Bodkin JA, Cohen BM. Severe adverse interaction between pethidine and selegiline. *Lancet* 1991; 337(8735):246.
52. Spencer GT, Smith SE. Dangers of monoamine oxidase inhibitors. *Br Med J* 1963; 5332:750.
53. Codd EE, Shank RP, Schupsky JJ, et al. Serotonin and norepinephrine uptake inhibiting activity of centrally acting analgesics: Structural determinants and role in antinociception. *J Pharmacol Exp Ther* 1995;274(3):1263–1270.
54. Gillman PK. Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity. *Br J Anaesth* 2005;95(4):434–441.
55. Browne B, Linter S. Monoamine oxidase inhibitors and narcotic analgesics: A critical review of the implications for treatment. *Br J Psychiatry* 1987;151:210–212.
56. Papakostas GI, Nutt DJ, Hallett LA, et al. Resolution of sleepiness and fatigue in major depressive disorder: A comparison of bupropion and the selective serotonin reuptake inhibitors. *Biol Psychiatry* 2006; 60(12):1350–1355.
57. Shulman KI, Walker SE, MacKenzie S, et al. Dietary restriction, tyramine, and the use of monoamine oxidase inhibitors. *J Clin Psychopharmacol* 1989;9(6):397–402. ■